IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant: Al xander MacGregor

Serial No.: 10/006,740

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For: *HYDROSTATIC DELIVERY SYSTEM FOR CONTROLLED DELIVERY OF AGENT*

Art Unit: 3762

Examiner: Unassigned

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
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Arlington, VA 22202, on this date.

03/25/2002
Date

Robert Wickman

## PRELIMINARY AMENDMENT

Commissioner for Patents
Arlington, VA 22202

Dear Sir:

Preliminary to examination of the above-captioned patent application, please amend the application as follows. A marked up copy of the amended specification is attached to this amendment. A Declaration and a copy of U.S. Provisional Application Serial No. 60/251,751 accompanies this amendment.

**IN THE SPECIFICATION:**

Please amend the specification as follows:

**Please replace the paragraph on page 2, lines 7-11 with the following:**

Core embedding or core coated delivery systems have been disclosed, for example in U.S. 3,538,214. This document describes a diffusion-controlled device in which a tablet core containing the active ingredient, is surrounded by a water insoluble coating. The insoluble film coating has been modified with modifying agents that are soluble to the external fluids in the gastrointestinal tract.

**Please replace the paragraphs on page 3, line 30 through page 4, line 19 with the following:**

Additionally, some active agents posses chemical properties that are comparable in ionic strengths to those of strong electrolytes and salts commonly used as osmotic adjuvants. In these instances, and due to different pH

environments in the gastrointestinal tract, agents comprising significant ionic strength will manifest varying degrees of ionization that may compromise the predictable performance of the osmotic device. Osmotically active therapeutic agents with ionic strengths comparable to that of osmotic adjuvants, and that are localized within osmotically driven devices, will act as osmotic agents and enhance the osmotic influx of water from the fluid environment. Similarly, agents having high ionic strength may also cause variations in the osmolarity of the adjacent fluid environment upon their release from the delivery device. Therefore, osmotically-driven devices comprising agents characterized as having a high ionic strength, lack self-regulation.

A delivery system that is not readily influenced by minor changes to its physical form, intrinsic properties of an active agent (e.g. ionic strength), or variables in the environment of use (e.g. varying osmolarity of the human gastrointestinal tract and factors such as the dietary contents), can be reliably programmed to deliver the agent in a pre-determined manner with increased accuracy and precision. Therefore, there remains within the art a need for a reliable zero-order drug delivery system, where the release of an agent is independent of its own concentration, that provides controlled drug delivery of an active agent to an environment of use and that is independent of physiological variables of the environment of use, as well as the intrinsic properties of the active agent.

**Please replace the paragraph on page 13, line 27 through page 14, line 14 with the following:**

Additional agents of interest include quinoline and naphthyridine carboxylic acids and related compounds, such as 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid; 5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid; 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidine-6-carboxylic acid; 9-fluoro-6,7-dihydro-5-methyl-1-oxo-1H,5H-benzo[ij]quinoxolizine-2-carboxylic acid; 1-ethyl-1,4-

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dihydro-4-oxo-7-(4-pyridinyl)-3-quinolinecarboxylic acid; 1-ethyl-1,4-dihydro-4-oxo-[1,3]dioxolo[4,5-g]cinnoline-3-carboxylic acid; 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[ 1,2,3-de][1,4]benzoxazine-6-carboxylic acid; 1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-1,8-naphthyr idine-3-carboxylic acid; 1-ethyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxo-1,8-naphthyridine-3-carboxylic acid; 1-cyclopropane-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; 1-methylamino-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-ipiperazinyl)-3-qui nolinecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quino linecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl )-3-quinolinecarboxylic acid; 1-(4-fluoro-1-phenyl)-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid; and 1-ethyl-6-fluoro-1,4-Dihydro-4-oxo-7-(3-ethylaminomethyl-1-pyrrolidinyl)-8-fluoro-3-quinolinecarboxylic acid.

**Please replace the paragraph on page 17, lines 7-16 with the following:**

AA

- acrylic-acid polymers with cross-linking derived from allylsucrose or allylpentaerithritol, including water-insoluble acrylic polymer resins. Single compounds or a blend of compounds from this group of polymers include for example, but not limited to Carbopol.RTM.971-P, Carbopol.RTM.934-P, Carbopol.RTM.974P and Carbopol.RTM.EX-507 (GF Goodrich, or any other commercially available brand with similar properties, may be used). Preferably, the acrylic-acid polymers have a viscosity from about 3,000 centipoise to about 45,000 centipoise at 0.5% w/w concentration in water at 25°C, and a primary particle size range from about 3.00 to about 10.00 microns in diameter, as determined by Coulter Counter;

**Please replace the paragraph on page 17, line 31 through page 18, line 9 with the following:**

AS

Examples of methods of preparation, for example of Carbopol.RTM.934-P, - a polymer of acrylic acid lightly cross-linked with polyallyl ether of sucrose having an average of 5.8 allyl groups per each sucrose molecule, has been

A5 contd

disclosed in U.S. 2,909,462; 3,033,754; 3,330,729; 3,458,622; 3,459,850; and 4,248,857 (which are incorporated herein by reference). When Carbopol.RTM.971-P is used, the preferred viscosity of a 0.5% w/w aqueous solution is 2,000 centipoise to 10,000 centipoise. More preferably, the viscosity of a 0.5% w/w aqueous solution is 3,000 centipoise to 8,000 centipoise. When Carbopol.RTM.934-P is used, the preferred viscosity of a 0.5% w/w aqueous solution is 20,000 centipoise to 60,000 centipoise, more preferably, the viscosity of a 0.5% w/w aqueous solution is 30,000 centipoise to 45,000 centipoise.

**Please replace the paragraph on page 19, lines 15-20 with the following:**

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- single compounds or combinations derived from cross-linked N-vinyl-2-pyrollidone (PVP) selected from a group of chemically identical polyvinylpolypyrrolidone such as Polyplasdone.RTM.XL, Polyplasdone.RTM.XL-10, Polyplasdone.RTM.INF-10 (International Specialty Products). Preferably, the cross-linked N-vinyl-2-pyrollidone has a particle size from about 9 microns to about 150 microns; and

**Please replace the paragraph on page 24, lines 13-22 with the following:**

A7

Without wishing to be bound by theory, at a given point of net imbibed water, there is a given ratio of the number of hydrated group-A particles and expanded particles or molecules of the rapid expansion-group-B particles, that creates a positive differential pressure. This hydrostatic pressure acts against the influx of water and at some point the inflow of water will equal the outflow of water. The resultant hydrostatic volume efflux overwhelms the passive diffusive volume efflux within the delivery system. When the inflow and outflow of water become equal, the system manifests a dynamic constant volume and surface area. This results in a steady state release of solved or partially solved particles of the agent of interest along with any other adjuvant.

**Please replace the paragraph on page 25, lines 11-31 with the following:**

A8

In the hydrostatic delivery system of this invention, the presence of a hydrostatic couple creates a positive hydrostatic pressure within the delivery

A8 contd

system as a result of the differential rates of volume expansion between the group-A and group-B components. This differential pressure opposes the volume influx of the imbibed fluid and reduces the volume gain of delivery system. The volume efflux due the hydrostatic pressure $(dV/dt)_h$, is substantially greater than the contribution to volume efflux as a result of passive diffusive flux. At an optimal level, which may be determined by a mathematically predictable ratio of the components of the hydrostatic couple, the rate of volume efflux approaches and eventually equals the rate of volume influx. This represents a dynamic steady state with a zero net increase in volume and a constant surface area of the delivery system (see Figure2). The one or more agents of interest that are dissolved or partially solved within the delivery system, are thus released at a rate determined by the total (net) efflux controlled and determined by hydrostatic pressure within the delivery system. The insignificance of the passive diffusive contribution to the net volume efflux proffers a delivery system whose performance is independent of the chemical concentration gradient of the agent of interest. If the volume within the delivery system is such that the total concentration of the agent of interest is above its saturation concentration, the resultant release of the agent of interest will exhibit a zero or near zero order kinetics. The net volume flux in the hydrostatic delivery system is represented by the following equation (equation 2):

**Please delete pages 29 through 31.**

**Please add between pages 28 and 32 the following:**

A9

| | | |
|---|---|---|
| Group-B | Crospovidone XL-10 | 8 |
| Flow promoter | Colloidal Silicon Dioxide | 4.3 |
| Lubricant | Magnesium Sterate | 3.67 |

The prepared delivery systems were placed within PBS at pH 7.0 in a Type II USP 24 Dissolution apparatus at 37°C (±0.5) using a paddle speed of

50 rpm. Caffeine release from the delivery systems were measured over time. Caffeine release was determined spectrophotometrically @ 272nm.

Method for Measuring Dynamic Volume Change due to Fluid Imbibition

The dynamic volume change of a fluid-imbibing or swelling tablet was measured by computation of the density of the swollen tablet and its mass. The basic relationship is:

$$Vt = Mt/D$$

Where Vt is the volume at a given time; Mt, is the mass of swollen tablet at a given time; and D, is the density of the swollen tablet

To obtain dynamic volume values, the same tablet undergoing swelling in the fluid media was removed from the dissolution media at regular (pre-fixed) time intervals, weighed in air (to obtain its mass) and weighed submerged in the fluid media (to obtain its buoyancy). The tablet is immediately returned to the dissolution media where swelling resumes. The time lapse between removal from the fluid media and its return to the media is kept constant and short in order to minimize errors due to excessive dehydration. This time interval is typically not more than 30 seconds.

The density of the swollen tablet is obtained by calculating:

$$\rho 2 = (A/P) * \rho o$$

where, $\rho 2$ is the density of the swollen tablet; $\rho o$ is the density of the fluid media.

Equipment & Materials for Dynamic Volume Measurement

Swelling & Drug Dissolution Measurements

USP Dissolution Apparatus Type II (Paddle)

Settings: Rotational Speed: 40 – 50 rpm

Temperature: 37° C +/- 0.5°C

PBS buffer pH 7.00 (or suitable buffer at a desired pH).

Dynamic Volume Measurements

Mettler-Toledo Density Determination Kit (for liquids and Solids) Model # 33360

Media: PBS buffer pH 7.00 or suitable buffer at a desired pH.

Figure 1 shows a plot of the dynamic volume profile of a prior art formulation, demonstrating a linear volume increase associated with a hydrodynamic polymer (Group- A component). The corresponding drug release (dissolution profile) for this formulation is shown in Fig 3. A rapid release (exponential) of an agent of interest from the prior art delivery system, reaching a maximum release rate after about 3.5 to 4 hours is evident in Figure 3. This is the typical Fickian release manifested by prior art compositions using group A-type components as the control release polymer. With this delivery system, the rate of efflux of an agent of interest is due to passive diffusion and is substantially less than the rate of influx of the fluid. Consequently, the rate of release of an agent of interest is dependant on the chemical potential and concentration of the agent.

The dynamic fluid profile of a delivery system of the present invention comprising a hydrostatic couple provided in Table 1 is presented in Figure 2. Following an initial increase in the dynamic volume of the tablet, the volume remains stable over time wherein the influx of fluid is equal to the efflux of caffeine. This represents a controlled increase in the dynamic profile of a tablet, which reaches and maintains a maximum volume after a period of time (depending upon the ratio of the hydrodynamic fluid-imbibing polymer, to hydrostatic pressure modulating agent). Figure 4 shows the corresponding drug release (dissolution profile) for a formulation comprising a hydrostatic couple of the present invention, and displays a linear, zero-order release of an agent of interest for over 16 hours. Figures 2 and 4 demonstrate how the volume increase in a delivery system comprising a hydrostatic couple is reduced, resulting in an increased and continuous efflux rate. Because the rate of efflux of the agent of interest is independent on the concentration of the agent but dependent on the hydrostatic pressure within the delivery system, the kinetics of agent release is zero-order.

**Examples 3-6:**

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In these examples hydrostatic delivery systems for extended release formulation of various therapeutic agents are presented. Two formulations (Formula 1 and Formula 2) are used to illustrate how the hydrostatic couple as described herein can be used to achieve zero-order kinetics and predictably different release rates. Formula 1 exhibits faster rates of drug release than that observed with formula 2. The rate of release of the agent of interest may be selected considering several variables, for example, but not limited to the solubility of the agent of interest, and pharmacological activity of the agent of interest. For example, with decreased solubility of an agent of interest, faster release of the agent may be desired, such as that provided by, but not limited to, Formula 1. In the case of a soluble agent of interest, slower release of the agent from the delivery system may be desired, for example, but not limited to, using a hydrostatic couple as provided in Formula 2. It is to be understood, however, that the formulation of the hydrostatic couple may be varied as required to obtain a desired rate of release of an agent of interest.

Example 3 : **Extended Release Theophylline 80 mg**

**Table 2: Extended Release Theophylline**

| Components | Formula-1 | Formula-2 |
|---|---|---|
| Theophylline USP | 80.00 mg | 80.00 mg |
| Carbopol 971P NF | 320.00 mg | 320.00 mg |
| Crospovidone XL-10 | 6.40 mg | 0.00 mg |
| Crospovidone INF-10 | 0.00 mg | 6.40 mg |
| Sodium Lauryl Sulphate NF | 4.00 mg | 4.00 mg |
| Colloidal Silicon Dioxide NF | 3.00 mg | 3.00 mg |